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Resistance all round

There is no doubt that the big talking point in antimicrobial circles these days is resistance. In cancer chemotherapy resistance to therapy has also become a major area of concern. Among infection doctors, there is also talk of the 'End of the Antibiotic Era', but I wonder if these concerns might be too pessimistic. How bad is the situation?

Infections in the hospital

One problem in determining the scale of antibiotic resistance is that most research on prevalence is carried out in university hospitals where resistance can be seen at its extreme manifestation. The same situation with regard to sampling occurs in developing as in industrialized nations. In the main university centres of medical activity, the most complex and vulnerable patients are treated and the microbiology research facilities are at a high level. This means that the majority of resistant organisms get a good deal of publicity. It is in the most advanced hospitals that the edge of therapy is approached. It is here that vancomycin-resistant enterococci are seen, where multi-resistant Gram-negative rods abound and spread, and where *Staphylococcus aureus* of intermediate resistance to glycopeptides are beginning to emerge.

It is also in the largest hospitals that the newest and broadest spectrum antibiotics are used. Criticism of this heavy usage has to be tempered by the fact that the patients being treated in these hospitals are in categories that are most likely to be infected by multi-resistant strains. However, the need for more informed usage – more specific usage – of antimicrobials is generally acknowledged.

In smaller hospitals, long-term healthcare facilities and nursing homes, sick people can be gathered together without major antibiotic resistance limiting the relatively low-tech antibiotic therapy that is required. It is true that *S. aureus* does spread from time to time in such facilities, but infection problems with other resistant bacteria, such as *Stenotrophomonas*, *Acinetobacter* and *Enterococcus faecium* are uncommon. Susceptibility is not as exciting to journal editors as is resistance; it may be more difficult to have papers on the absence of resistance published, but more information from such hospitals would perhaps serve to allay fears of universal difficulties in antibiotic use.

Infections in the community

Community infections are, in the main, poorly served by those who carry out resistance surveys. Even the commonly studied respiratory and urinary pathogens are strains isolated

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Amsterdam, The Netherlands – venue for the 22nd International Congress of Chemotherapy (30 June–3 July 2001).

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From the ISC President

My 4-year period with the honour of serving as the President of the International Society of Chemotherapy (ISC) is coming to a close at the 22nd ICC in Amsterdam (30 June–3 July 2001). Professor Jean-Claude Pechère from Geneva is taking over, after a period as the ISC Secretary-General.

The ISC Secretariat

During the past 4 years, there have been several positive developments. The most important was establishing a central Secretariat. This is presently located in London, with an address rather suitable as a reflection of the Viking heritage of the current ISC President. Saint Olav was a Viking king who managed to unite all the provinces that became Norway. King Olav was converted to Christianity in England and brought the religion back to Norway – imposing it on his subjects who were forced to abandon the multiple gods of the Viking religion. One such god was Thor – few are aware of how he is reflected in everyday English, and in all Scandinavian languages: Thursday is named after Thor!

The ISC Secretariat is managed by Faridah Moosdeen from Malaysia and, more recently, Jamaica. She left the position of the ISC Honorary Treasurer to devote more time to the ISC. We are grateful for her diligence that has enabled the ISC to focus more than otherwise on organizational matters that require continuity, which had been possible during the past 2 years.

The *International Journal of Antimicrobial Agents*

The Society has published the *International Journal of Antimicrobial Agents (IJAA)* together with Elsevier during the past 3 years. The Journal is ably led by Professor JD Williams, as Editor-in-Chief. This has enabled us to publish scientific papers contributed from around the world. The status of the Journal has developed over the years while it has been with the ISC, and I hope it continues to do so.

Antibiotics Chemotherapy

Another important contribution is the Newsletter. This started with the initiative from David Williams who was one of the editors. In this fifth year of publication, the previous editors need to be rested, although Faridah Moosdeen will retain responsibility for the Newsletter's management. I would like to wish the new editors, Kurt Naber, Bob Sidwell and Victor Lim all the best.

Organization of the ICCs

One downside in the past 4 years has been the number of delegates attending the International Congress of Chemotherapy (ICC). After the record number of 11 000 when the Scandinavian Society of Antimicrobial Chemotherapy organized the ICC in Stockholm in 1993, there have been smaller numbers subsequently: in Montreal, Sydney and in Birmingham. To maintain continuity and uniformity of ICC, we see it as vital that the ISC takes primary charge of the organization of the ICCs and not out-source this role – as has been the trend.

The 23rd ICC – South Africa, June 2003

The ISC will be taking charge of the organization of the 23rd ICC, to take place in Durban, South Africa from 8–11 June, 2003. The host Member-Society in Durban will be the Infectious Diseases Society of Southern Africa. We have now also – after a long process of tenders and evaluations – chosen Congrex as our official professional congress organizer (PCO). Congrex have been tried and tested at several European Congresses of Chemotherapy – from the 1st ECC in Glasgow, followed by Hamburg and Madrid, to Paris in 2002. They played a major role in the International AIDS meeting in Durban and their experience will serve the 23rd ICC well.

In 2005, the ICC will be held in the Philippine capital, Manila. The PCO also has an international network of offices and we hope this will be an asset to our aim of organizing congresses all around the world.

Enlargement of the ISC

The ISC network has been enlarged by a further 10 Member-Societies during the past 4 years. One development has been to strengthen the ISC's presence in Africa. At the 12th Mediterranean Congress of Chemotherapy in Marrakesh, Morocco, in November 2000, the African Society of Chemotherapy was established, thanks to the initiative of J-C Pechère. This is the second society in Africa – after the Infectious Diseases Society of Southern Africa – which will be a cornerstone at the 23rd ICC in Durban.

Professor Tom Bergan – President of the ISC.

I look forward to further development of the ISC and am thankful for the opportunity to have served for 8 years as Secretary-General and for 4 years as President. My best wishes for their efforts go out to the Administrative Secretary, the future President, J-C Pechère, the future Vice-President, Joichi Kumazawa, the future Secretary-General, Kurt Naber, and the Honorary Treasurer, who remains as Erdal Akalin.

Tom Bergan

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from patients in urban areas around major hospitals where facilities exist to carry out such studies. How prevalent are antibiotic-resistant *Streptococcus pneumoniae* in rural areas? Do children in better social and less-crowded conditions have such a high carriage rate as those in deprived urban areas? The numerous reports on this subject are heavily biased towards the university hospital catchment areas. In developing countries these hospitals may be the only areas in the country where such studies can be carried out.

Adequately controlled studies

A further influence on the reporting of antibiotic resistance is that it may be difficult to find patients who can be sampled before antibiotics have been administered. Patients admitted to hospital with community-acquired pneumonia may already have had the benefit of several days of penicillin therapy before admission. In urinary tract infection, the situation is made more complex by the recommendation that patients should have their urine cultured only as a 'test of cure' after receiving antibiotics. This ensures that antibiotic-resistant strains have a major advantage in getting into the statistics. It is necessary in these circumstances to publish some studies where an 'uninterfered-with' series of patients is sampled before antibiotics are given. Then, we will be able to state with more confidence the true level of resistance prevalence.

JD Williams
London, UK
Guest Editorial

Role of the experimental animal in antibiotic research ~ Presented at the 3rd ECC, Madrid, Spain in May 2000

C Carbon

Therapeutic implications of global warming and other potential disasters in the 21st Century ~ Presented at the 3rd ECC, Madrid, Spain in May 2000

AM Geddes

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the stratosphere due to CFCs, which were only introduced in the 1930s, causes an increase in the amount of ultraviolet B radiation reaching the earth from the sun. These factors have contributed to an increase both in the overall 'canopy' which keeps the earth warm, and also in the amount of heat reaching the earth from the sun. The result is a warmer planet.

What could be the consequences for infection, and therefore chemotherapy, of global warming as described above? Possibly surprisingly, in view of the relatively minor predicted changes, the consequences could be dramatic! The following could result, especially in countries with temperate climates:

- Warmer summers and less cold winters;
- Droughts leading to crop failures;
- Higher sea levels due to polar ice melting leading to flooding;
- Geographical migration of insect vectors of infectious diseases.

As a result of these factors, there could be changes in the geographical range and incidence of vector-borne diseases such as malaria and also in water-borne infections. In addition, new infections, especially zoonoses, may appear. Such changes could lead to a requirement to re-assess priorities for new antimicrobial agents, especially if microbial resistance is an associated phenomenon.

Conclusions

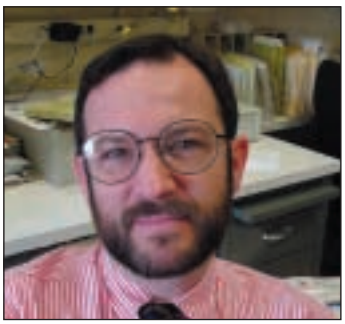
Global warming is only one of the potential disasters that could influence infectious diseases and chemotherapy in the 21st Century. Others include bioterrorism and the advent of new zoonoses not necessarily related to climate change. Increased travel will add further pressures to the incidence and distribution of infectious diseases, including those that are resistant to available antimicrobial chemotherapy.

Greenhouse gases

CO_2, carbon dioxide
CH_4, methane
N_2O_2, (dimeric gaseous) nitric oxide
CFCs, chlorofluorocarbons
HCFCs, hydrochlorofluorocarbons
HFCs, hydrofluorocarbons

Interferon gamma, its receptors and susceptibility to infection ~ Presented at the 3rd ECC, Madrid, Spain in May 2000

SM Holland



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE, BETHESDA, USA

Dr Holland works from the Laboratory of Host Defences at the US National Institute of Allergy and Infectious Disease, where he is Head of the Immunopathogenesis Unit. His research uses molecular methods to elucidate the pathogenesis of infectious disease.

Mycobacteria infect macrophages, stimulating the production of interleukin 12 (IL-12), which, in turn, acts on lymphocytes to stimulate the production of both IL-2 and interferon gamma (IFN-γ). IFN-γ acts through its receptor to upregulate tumour necrosis factor alpha (TNF-α), upregulate IL-12 and kill intracellular parasites, including mycobacteria and salmonellae. Therefore, IFN-γ controls its own expression through regulation of IL-12. The counter-regulatory pathways (e.g. IL-10, tumour growth factor β [TGF-β]) involved in controlling IFN-γ production have not yet been identified as causing disease in humans.

Intracellular infections

The critical role for this complex circuit – at least where intracellular infections are concerned – is to increase IFN-γ. Patients with complete absence of the IFN-γ receptor (IFN-γR) due to autosomal recessive (AR) mutations in IFN-γR1 (the IFN-γ ligand-binding chain) or IFN-γR2 (the signal transducing chain) fail to form granulomata and most die with disseminated non-tuberculous mycobacterial infection (DNTM). In contrast, patients with AR defects in the IL-12 receptor β1 (IL-12Rβ1) or IL-12p40 retain a low level of IFN-γ production, which probably accounts for their improved survival and the ability of these patients to form morphologically normal granulomata. Patients with mutation in IFN-γR1 are much more common than those with mutations in IFN-γR2. Likewise, despite many reports of autosomal recessive mutations in IL-12Rβ1, no defects have yet been identified in IL-12Rβ2. The reasons for these biases are not yet clear, and may reflect biases in referral, survival or organism susceptibility. The most prevalent group of patients with IFN-γR defects are those with autosomal dominant IFN-γR deficiency caused by a mutational hotspot in the IFN-γR1 gene (chromosome 6). These patients have excess extracellular domain of IFN-γR1 which is devoid of the intracellular signalling domain. This leads to accumulation of immunoreactive IFN-γR1 on the cell surface which is easily detected by flow cytometry. These mutant receptors are able to bind IFN-γ but not transduce signals through it.

Patients with defects in IL-12Rβ1 or IL-12 production as well as those with autosomal dominant IFN-γR1 are successfully treated for DNTM infection with IFN-γ along with antimycobacterials. The mechanisms that mediate IFN-γ's activity against intracellular infections are still not clearly defined, but candidate activities include increased antigen processing and presentation, lowering of intravacuolar pH, increased production of superoxide and its downstream metabolites, decreased prostaglandin E2 production, and increased intracellular antibiotic concentration.

Recently, increased susceptibility to herpesvirus infections and respiratory syncytial virus (RSV) has been observed in patients with IFN-γR defects, fulfilling the expectations generated from mouse models.

The role of IFN-γ in preventing infection with non-tuberculosis mycobacteria (NTM) in normal hosts is somewhat different from its activity in the treatment of established infections. IFN-γ treatment of leprosy and leishmaniasis only leads to reduction in microbial burden when IFN-γ is given in conjunction with antimycobacterials or antiparasitics – no reduction in infectious burden is noted when IFN-γ is given alone.

Future directions

The potential human applications of IFN-γ are still largely undeveloped. The only licensed US uses are of IFN-γ in the prophylaxis of infections in chronic granulomatous disease, a phagocytic disorder not associated with any kind of IFN-γ deficiency and osteopetrosis. Trials showing human clinical therapeutic benefit from IFN-γ have been completed in leprosy, leishmaniasis and DNTM. Studies in the treatment of pulmonary NTM and tuberculosis with either systemic or aerosolized IFN-γ are underway.

Acridines ~ time for another look?

Forgotten forerunner

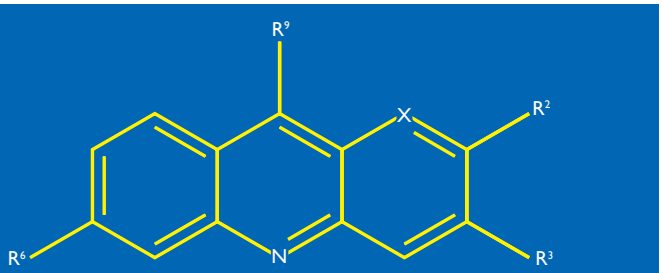
During the era of antimicrobial chemotherapy there have been many different drugs employed – based mainly on sulphonamides, penicillins and cephalosporins, fluoroquinolones and now the oxazolidinones. Many of those involved in the highly active and forward-looking pharmaceutical industry forget that antimicrobial chemotherapy on a large scale began, not with any of the above-mentioned classes, but with a humble, inexpensive aniline dye.

The exigencies of massive battle casualties during the First World War saw the use of two dyes in allied base hospitals in wound disinfection:

- Triarylmethane Brilliant Green;
- Proflavine (3,6-diaminoacridine; see Figure 1).

These basic (cationic) dyes were antibacterial and had been discovered in earlier work by Ehrlich, but their introduction at this vital time was due to one of his students, Carl Browning. Wound disinfection, even in complicated presentations, was shown to be easily achievable using proflavine, and many lives were saved.

Research on the acridines and their derivatives was continued mainly in post-war Germany, and the evolution of many modern drugs can be seen from therapeutics such as chloroquine, atebrin (Figure 1) and chlorpromazine. These drugs are derivatives resulting from the chemical functionalization of simple azine dyes such as proflavine. Although the Second World War saw the widespread use of aminoacridines such as proflavine and aminacrine (9-aminoacridine; Figure 1) in battle casualties, these were eclipsed by the large-scale introduction of penicillin in 1944 and have never since enjoyed the same level of use.



	X	R^2	R^3	R^6	R^9
Proflavine	CH	H	NH_2	NH_2	H
Atebrin	CH	OCH_3	H	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$
Aminacrine	CH	H	H	H	NH_2
Ethacridine	CH	OC_2H_5	H	NH_2	NH_2
Azacrine	N	OCH_3	H	Cl	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$

Figure 1: Chemical structures of acridine drugs.

Feared side-effects of acridines

One reason for the fall from grace of the acridines lies in their mode of action: intercalation of nucleic acid by the cationic chromophore interrupts bacterial cell replication – the simple aminoacridines are bacteriostatic. The correlation between antibacterial efficacy and cationic ionization coupled with sufficient planar surface area was made by the Australian chemist Adrien Albert in the 1940s. However, there are several modern acridine anticancer drugs (e.g. amsacrine) which interfere with topoisomerase II activity in mammalian cells, and there is the assumption that acridine antibacterials will cause DNA damage in the host. Such activity – *in animals* – has never been reported, but the risk of such side-effects seems sufficient to bar all but a few acridines from clinical usage: proflavine cream still appears in pharmacopoeias and ethacridine lactate, invented in Germany in 1920, is a constituent of several preparations for travellers' diarrhoea.

More promising acridine derivatives

The fact remains that the acridine chromophore has many more derivatives to offer, in terms of putative antimicrobials, than most other established drug types – mainly due to the ease and scope of functionalization of the chromophore. Increased antibacterial activity, for example, can be found in alkyl- or halo-derivatives of the simple aminoacridines; functionalization of the amino groups has led to more potent compounds. Chromophoric alteration has also been successful, e.g. the inclusion of a second ring nitrogen – as in azacrine. Such data is readily available in the literature.

There is scant evidence to suggest that many acridine derivatives were tested as systemic antibacterial agents, although scientists in Bayer were working on this in the 1930s. Acridines have been used mainly topically, and it may be more attractive in the short-term to employ them in cleansing traumatic or post-operative wounds until toxicity worries have been allayed. In addition, it is unlikely that penicillin-binding proteins would be effective in combating acridines. The author's group has shown that related phenothiazinium compounds are equally effective against methicillin-sensitive as well as methicillin-resistant *Staphylococcus aureus*.[1] Hence, the use of aminoacridines such as proflavine in drug-resistant infections is also warranted.

It may be that the acridines are not the answer in overcoming the current levels of infection in our hospitals, but have we really asked the question?

Mark Wainwright.

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Infectious Diseases Visiting Fellowship in Malaysia

(Malaysian Society for Infectious Diseases and Chemotherapy)

The Malaysian Medical Association Foundation Infectious Diseases Fund Visiting Fellowship Programme (which was launched in early 2000) provides for three fellowships annually. Recipients of the fellowship will be provided with an economy return flight, hotel accommodation and RM150.00 per day, and are required to conduct workshops or training courses on infectious diseases over a period of 2–3 days or longer in Malaysia. The visiting fellowship is open to all, and anyone interested is requested to send a detailed CV and indicate their areas of speciality to: The Secretary, Malaysian Society for Infectious Diseases and Chemotherapy, Department of Microbiology, Hospital UKM, Jalan Yaccob Latif, 56000 Kuala Lumpur, Malaysia.

Twenty years of clinical pharmacology in Beijing

A modern Institute of Clinical Pharmacology was set up in Beijing in 1980. There were two main sections, one on anti-infectives, and the other on drugs affecting the brain. Both sections have had remarkable success in establishing a leading role in the use of drugs that impinge upon the inhabitants in the most populated country in the world.

The Director of the Institute of Clinical Pharmacology at Peking University* is Professor Jia-Tai Li who has been an active member of the International Society of Chemotherapy since 1981 and served on the Executive Committee for 6 of those years. She also played a major role in establishing the Western Pacific Society of Chemotherapy. It was, therefore, fitting that the 20th anniversary of the Institute of Clinical Pharmacology coincided with the Beijing International Symposium on Antibiotics (BISA) – a satellite meeting of the 7th Western Pacific Congress on Chemotherapy and Infectious Diseases (WPCCID; see page 10).

The birthday party took place following the BISA meeting and was more of a family affair than an international event. Apart from the high-ranking officials presented, about 200 people attended and included former staff members and collaborators. It was a very happy occasion to see many people from the early days of the development of the Institute and former colleagues who have moved on to success elsewhere.

There were several short laudatory speeches before Professor Li outlined the progress of the Institute and presented all with an excellent nostalgic photographic history of the Institute. Our congratulations from the Newsletter to Professor Li and colleagues. A lot of history can take place in 20 years when the achievements have been so great.

JD Williams
London, UK

Delegates at the 20th anniversary of the Institute of Clinical Pharmacology. Seated on the extreme right is Professor Jia-Tai Li, the founder.

*Beijing and Peking are the same place but the names are not interchangeable. In some circumstances, Beijing is used and in some, Peking. Please do not ask for explanations.

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Australia

Richard O Doehring.

enough to be used by patients and their carers.[7]

OPAT is an exciting concept, promising great benefits to patients and stretched healthcare resources alike. My letter, however, is a plea to consider first what drugs are clinically, microbiologically and ecologically appropriate, and then to choose the setting in which they are given.

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Letter to the Editors

SIRS ~ Dr Alan Tice[1] makes a strong case for outpatient parenteral antimicrobial therapy (OPAT), on grounds of patient comfort, social functioning and cost containment.

Are iatrogenic infections reduced by OPAT? A major risk factor for hospital infections remains the intravenous line.[2] The hospital is a place of invasive interventions and vulnerable patients. Replicate this in the home, and we will replicate the hazards.

Particular cause for concern is how treatment is chosen. Dr Tice's article shows just one drug, ceftriaxone, accounting for around 40% of antimicrobial use in OPAT. Cellulitis, commonly due to streptococci, is at the top of the list of conditions treated – yet penicillin, still the drug of choice, does not make it to the top 10 antibiotics in OPAT.

Is this prudent therapy? For almost all the indications for which ceftriaxone might be expected to be used in OPAT, a narrow-spectrum alternative exists.

There is abundant evidence that exposure to third-generation cephalosporins creates a risk for acquiring problem organisms, including vancomycin-resistant enterococci,[3] methicillin-resistant *Staphylococcus aureus*,[4] resistant Gram-negative bacilli[5] and *Clostridium difficile*.[6]

Once-daily dosing need no longer be a consideration. Even continuous infusion, theoretically to be preferred for the β-lactams, can be achieved with devices simple and safe

Functional foods, nutraceuticals and herbal medicines versus infection

Even before the implementation of religion-driven hygienic practices, the human race had developed and proliferated. Balanced nutrition and good hygiene are sufficient to ensure limited infant mortality, growth and a healthy life-span currently exceeding 40 years without resorting to medical care; this situation presently applies to hundreds of millions of people worldwide.

The vast majority of people can only afford to pay a maximum of US$5 a year each on healthcare. They resort to foods, supplements, herbals and faith to fight symptoms and diseases, extend life expectancy and improve quality of life. In industrialized societies the cost, side-effects and overall image of pharmaceuticals has provoked a renewed interest – and major expenditure – in 'natural' products, i.e. functional foods, nutraceuticals and traditional or herbal medicines. While most are immunomodulators or immunostimulants, many are directly anti-infective.

Functional foods

Ten categories of foods are currently accepted by the US Food and Drug Administration (FDA). Examples of anti-infective functional foods are: dairy products, e.g. yoghurt,[1] lactoferrin,[2] those containing *Lactobacillus casei* species *GG*[3] and Actimel®;[4] xylitol;[5] green tea; and cranberry juice.

- Probiotics – beneficial bacteria which favourably alter the intestinal microflora and inhibit the growth of harmful bacteria, e.g. *Lactobacillus acidophilus*, bifidobacteria – are largely represented.
- Prebiotics – a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health, e.g. oligofructopolysaccharides – however, are used against intestinal or gastrointestinal-borne infections.

Nutraceuticals

The direct antibacterial, antifungal or antiviral effects of commercial nutraceuticals (such as vitamin C and zinc lozenges) are less convincing. Most claims are indirect: the 'active' products seem to be 'working' via the immune system.

Herbals

The catalogue of herbals is extremely rich. Most Chinese herbs are not prescribed individually and are used as part of a holistic approach to the patient. *Qingliao/Chinghao* (Artemisinin) extracted from *Artemisia annua* is currently the best antimalarial drug available.[6]

Many individual herbs are clinically active against bacterial, fungal or parasitic diseases; others demonstrate promising *in vitro* activities. The problem with herbs can be referred to as '*the six-Ss*':

- Selection is unknown;
- Sourcing is variable and difficult to trace;
- Structural analysis is virtually non-existent;
- Standardization is quasi-unknown and opposed;
- Studies are few, with poor protocols;
- Safety, which is highly questionable.

Placebo effects and pleasure

A major contributor to the optimized anti-infective immune response, however, is *pleasure*, be it as a positive contribution in daily life, or as a *placebo* effect.

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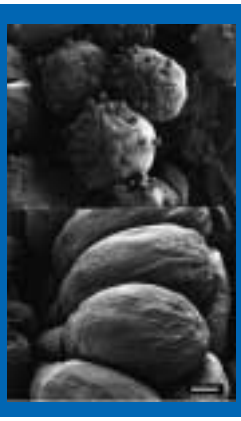
Chinese Herbs with Antimicrobial Activity

Herb	Antimicrobial activity
Forsythia	Versus *Staphylococcus aureus*
Puffball	Versus *Staphylococcus aureus*
Honeysuckle	Versus *Salmonella typhi*
Chinese Goldthread Rhizome	Furuncles, boils
Greenbrier Rhizome	Leptospiriosis, syphilis (brain)
Houttuynia cordata	Versus *Streptococcus pneumoniae*
Isatis tinctoria	Cholera, typhoid
Umeboshi plum	Versus *Shigella sonnei*
Cranberry	Versus *Escherichia coli* (urine)
Uva ursi	Versus *Escherichia coli* (urine)
Tea-tree oil	Potent wide antiseptic



Sweet Wormwood

(*Artemisia annua* L)

- SEM micrographs of qinghao
- Top: artemisin-rich glandular trichomes
- Bottom: glandless

Courtesy of Anthony L Almada.[6]

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In 1985, he was awarded the Medal of Vermeil by the city of Paris for his outstanding contributions to medicine. He has published extensively and worked in different countries. He currently holds a part-time position at the University of Hong Kong. He also actively consults with pharmaceutical, diagnostic and nutraceutical companies, as well as for the food, wine and water industries. He currently focuses his research on the positive role of pleasure.

News from the 7th WPCCID

7th Western Pacific Congress on Chemotherapy and Infectious Diseases, Hong Kong, 11–14 December 2000

A great success for the Western Pacific Society of Chemotherapy (WPSC; established in 1989 and just reaching adolescence) was its 7th Congress. The programme, put together by Wing-Hong Seto, Elizabeth Houang and John Peiris measured favourably with the best of other international congresses. It was very heartening to see 35 symposia and workshops with presentations made by worldwide experts. In addition, there were nine key-note lectures, five state-of-the-art lectures and seven Western Pacific 'topical' lectures. The Western Pacific perspectives dealt with the Hong Kong influenza and the Malaysian Nipah virus outbreaks, the problems of Epstein–Barr virus, antibiotic resistance and clinical trials in China, keratitis and contact lens, and zoonotic infections. We can all learn from these situations. Added to these are the 'industrial sessions' that address resistance and new antibiotics.

There were enough varied topics to satisfy the participants. There was a large Chinese contingent from the mainland, for some their first foray into the Western Pacific Congress. We hope this experience will whet their appetite to attend future congresses in the area and help in the transmission and exchange of knowledge. The knowledge that the 'Western' world brings to the Far East will also be useful and be put to good use.

The meeting platform for the Western Pacific region is the Western Pacific Congress. The next will be held in Perth, Australia in December 2002 and will indeed be a forum to discuss, share and ultimately resolve issues that concern the Western Pacific – the very objective for which the WPSC was set up.

F Moosdeen
London, UK

Over to Perth, Australia for the 8th Congress.

Opening ceremony of the Congress.

A young investigator awardee.

Pre-congress Academic Exchange, Guangzhou, 9–10 December 2000

In conjunction with the Western Pacific Congress on Chemotherapy and Infectious Diseases (WPCCID), the opportunity to address 'Hospital Infection and Cost Benefit' was taken by the Chinese Medical Association (represented by Professor Jing Yang), PLA Professional Committee for Hospital Infection (represented by Professor Shi-ping Chen) and the Asia Pacific Society of Infection Control (represented by Professor Wing-Hong Seto), who invited international speakers to address Hospital Infection in Guangzhou.

There were about 150 participants from mixed backgrounds – physicians and laboratory scientists attending the meeting. The international speakers included Allan Ronald (Canada) who spoke on nosocomial pneumonia, Michael Emmerson (UK) who discussed the optimization of microbiological services, and Tom Bergan (Norway) who tried to make predictions on antibiotic usage in the 21st Century. The strategy of antibiotic policy was presented by Dr Patricia Ching from Hong Kong. The delegates from Hong Kong also acted as Chinese interpreters. The contributions in the meeting were published in either Chinese (81) or English (70).

The five rams – symbol of Guangzhou.

The problem of emerging bacterial resistance in mainland China and the importance of surveillance was stressed in these presentations. The widespread use of new antibiotics as well as the cost of resistance was of great concern.

There was an opportunity for those from abroad to visit the First Military Hospital (of the PLA) in Guangzhou – also a medical university hospital. The facilities at the surgical unit were impressive, with the very best equipment. A special section is set aside for overseas paying patients who can make use of the latest, up-to-date diagnostic and therapeutic facilities. Chinese medicine, including acupuncture, complements Western medicine.

F Moosdeen
London, UK

International delegates in Guangzhou.

The Beijing International Symposium on Antibiotics – Post-congress of the 7th WPCCID, 16–17 December 2000

About 500 people participated in the Beijing International Symposium on Antibiotics that immediately followed the Western Pacific Congress in Hong Kong.

Although 80% of the participants were from China, the whole proceedings were conducted in English. This must be the first time a congress in China has been carried out without translation (apart from sponsored industrial sessions). Many of the speakers had never travelled outside the country, yet had prepared their material with great care to ensure the slides were clearly visible and the spoken delivery was quite understandable.

The big bosses of ISC and the Beijing and WESPAC Congresses – (left to right) Tom Bergan, Jia-Tai Li and Wing-Hong Seto.

Several of the speakers were presenting in English for the first time and made an excellent impact on the audience.

Many clinical trials of antimicrobials are now carried out in China and some differences are seen from Western procedures. Two points stand out. The first is the high degree of monitoring of the studies at all stages from inception, design, implementation and analysis. The second is the great emphasis placed on obtaining a definitive microbiological diagnosis before inclusion of the case in the analysis.

Those attending from China had the benefit of lectures from some well-known performers from Europe, USA, Japan, Australia and other countries in the Far East. The participants from outside China enjoyed a wide range of presented subjects, the sights and sounds of China and very warm welcomes. It is cold in December in Beijing.

To the pleasure of the international visitors the food was always Chinese, so we had the best of all worlds.

JD Williams
London, UK

Impact factors: use and abuse

The ISI®* Journal Citation Reports (JCR®*) impact factor has moved in recent years from an obscure bibliometric indicator to become the chief quantitative measure of the quality of a journal, its research papers, the researchers who wrote those papers, and even the institution they work in. This article (full text PDF can be found at: www.elsevier.com/locate/editors) looks at the limitations of the impact factor, how it can and how it should not be used.

What is an impact factor?

The *impact factor* is one of three standardized measures created by the Institute for Scientific Information (ISI) which can be used to measure the way a journal receives citations to its articles over time. The citation curve of any journal can be described by the relative size of the curve, the extent to which the peak of the curve is close to the origin, and the rate of decline of the curve. These characteristics form the basis of the ISI indicators *impact factor*, *immediacy index* and *cited half-life*.

How variable is the impact factor?

The impact factor is the most commonly used and also the most misunderstood measure. Its value is affected by sociological and statistical factors, such as the subject area, the type of journal, the average number of authors per paper, the size of the journal and measurement window.

Subjectivity: Fundamental subject areas have higher average impact factors than specialized or applied/clinical ones. The variation is so significant that the top journal in one field may have an impact factor lower than the bottom journal in another area. Comparisons of impact factors should therefore only be made for journals in the same subject area.

Article and journal type: There will be significant variation even within the same subject area according to the journal type or article type. Hence, care should be taken when comparing different journal types or journals with different mixes of article types.

Size: As the impact factor is an average value, it also shows variation due to statistical effects (see Figure 1). When impact factors are compared between years, it is important to consider the size of the journal. The impact factor of a journal of 140 articles would need to change by more than ±22% to be significant.

Why does impact variability matter?

Impact factors are easily affected by a host of conditions which do not directly impinge upon their principal use, a measure of the impact of publishing in a particular

continued on page 16

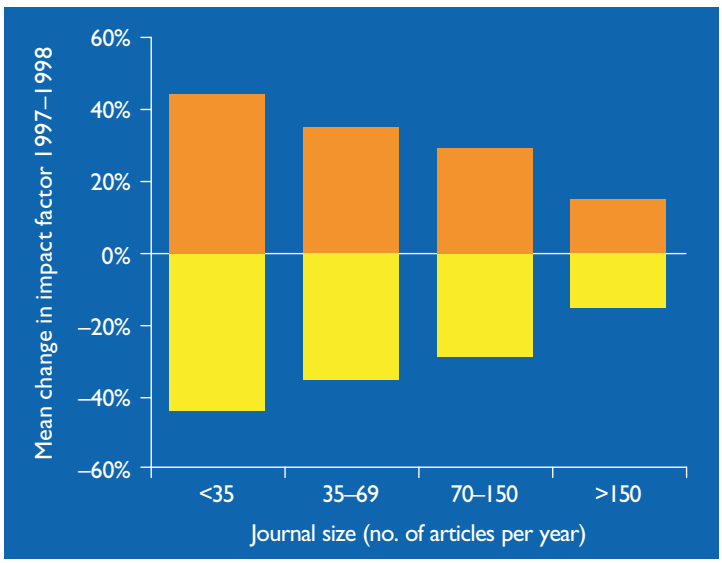

Figure 1: Impact factor fluctuation versus journal size. Based on sample of 4000 journals.

*ISI®, Journal Citation Reports and JCR® are registered trademarks of the Institute for Scientific Information, USA.

22nd ICC ~ Scientific Programme

Amsterdam 30 June–3 July 2001

The Scientific Committee has developed a scientific programme that encourages interdisciplinary communication and fosters global solutions to the challenges with which we are faced today. The topics listed here are some of those to be presented.

Saturday 30 June 2001 is the opening of this exciting Conference. Poster sessions, along with the exhibits, will be open all day Sunday, Monday and Tuesday, when the meeting ends. Posters will be displayed on-line as well as computerized on site.

Your participation at the 22nd ICC would be an excellent opportunity to share your work with the scientific community. This will be possible in a friendly atmosphere in a city and country that harbour so many exciting places to visit.

Andy IM Hoepelman
Chairman, Scientific Committee

PLENARY LECTURES

- How does the WHO react to the HIV-epidemic in the developing world?
- Malignancy and microbes: infection as a cause of cancer
- Gene therapy for severe combined immunodeficiencies
- Modelling in infectious disease
- Symptoms and suffering at the end of life in patients with cancer
- Molecular approaches to the development of new antimicrobials

SYMPOSIA

Oncology Track:

I. Angiogenesis

Anti-VEGF strategies – *G Jamson (UK)*
Angiogenesis and the immune response – *J Wagstaff (The Netherlands)*
Angiogenesis inhibitors and chemotherapy – *B Teicher (USA)*
The endostatin/angiostatin story – *tbc*
Vascular targeting – *E Voest (The Netherlands)*

II. Immunotherapy

DNA vaccines in heamatological malignancies – *tbc*
Tumour cell hybrid vaccination in advanced renal cell carcinoma – *A Kugler (Germany)*
Allogeneic mini-stem cell transplantation – *tbc*
Peptide vaccines – *tbc*
Targeting tumours with display-technology derived antibodies and peptides – *HR Hoogenboom (The Netherlands)*

III. Designer drugs

EGF receptor tyrosine kinase inhibitors – *G Blackledge (UK)*
Farnesyl transferase inhibitors: current status in clinical oncology – *FALM Eskens (The Netherlands)*
ADEPT & GDEPT – *R Begent (UK)*
Selective oestrogen receptor antagonists – *tbc*

IV. Cancer in developing countries

The cancer problem in the third world – *P Boyle (Italy)*
WHO essential drug programme and oncology – *HV Hogerzeil (Switzerland)*
Clinical evaluation of target based therapy – *S Nagahiro (Japan)*
Cancer chemopreventives from non-western medical cultures – *T-K Yun (Korea)*
Pharmacogenomics – *tbc*

V. Cancer care

Challenges in palliative care – *A de Graeff (The Netherlands)*
Oral antineoplastic agents – *HM Pinedo (The Netherlands)*
PET scanning in lung cancer – *HJM Groen (The Netherlands)*

Pumps everywhere: practical implications of basic science

Efflux in *Pseudomonas aeruginosa:* at the intersection of virulence and resistance – *T Köhler (Switzerland)*
Multidrug transporters in *Staphylococcus aureus:* does it matter for the clinician? – *GW Kaatz (USA)*
Practical implications of efflux systems in yeasts – *G Hogenauer (Austria)*
Drug resistance in *Plasmodium falciparum* – *tbc*
Clinical imaging of efflux in multidrug resistance of human cancer – *S Del Vecchio (Italy)*

Pharmacokinetics and pharmacodynamics

Use of pharmacodynamic principles in drug discovery – *MN Dudley (USA)*
Use of microbiology, animal models and computer modelling data for dose selection – *WA Craig (USA)*
Neonatal pharmacokinetics – *JN Anker (The Netherlands)*
Pharmacodynamics of antifungal agents – *GL Drusano (USA)*
Pharmacodynamics of the combination with artemisinin drugs for malaria – *PJ de Vries (The Netherlands)*

Viral infections

Parainfluenza: epidemiology and clinical impact – *tbc*
Treatment and prophylaxis modalities for RSV – *tbc*
The impact of adenovirus infections in the immunocompromised host – *M Horwitz (USA)*
HHV-6 and the immunocompromised host – *P Griffiths (UK)*
Enterovirus and pleconaril therapy – *J Romero (USA)*
Norwalk and the Sapporo viruses – *S Chiba (Japan)*

Influenza: new options for diagnosis, treatment and prevention

Influenza diagnosis: in from the cold? – *LA Wallace (UK)*
Flu and structure-based drug design – *RC Wade (Germany)*
Discovery and development of Oseltamivir – *tbc*
Treating and preventing influenza with neuraminidase inhibitors – *FG Hayden (USA)*
Intranasal flu vaccines – *R Gluck (Switzerland)*

Understanding and treatment of chronic hepatitis

Biological relevance of the genetic heterogeneity of hepatitis C virus – *P Farci (Italy)*
New targets for hepatitis C chemotherapy – *C Steinkuhler (Italy)*
A la carte treatment for chronic hepatitis C – *tbc*
Disease management of chronic hepatitis – *BS Schalm (The Netherlands)*
New insights in causes and treatment of hepatocellular carcinoma – *J Bruix (Spain)*

Pathogenesis of infections: the microbe

Evolutionary relationships of *Shigella, E. coli* and pathogenic enterobacteria – *PR Reeves (Australia)*
When bacteria talk to each other: quorum sensing in infectious disease states – *C Delden (Switzerland)*
Cryptococcus-induced inflammations – *A Casadevall (USA)*
Human listeriosis – *tbc*
Biological relevant events in the persistence of bacterial colonization or infection – *A Belkum (The Netherlands)*

Pathogenesis of infections: the host

The evolution of toll-like receptors – *tbc*
The role of toll-like receptors in the pathogenesis of infectious diseases – *tbc*
Apoptosis in immune cells: mechanisms and significance in infectious diseases – *G Dbaibo (Lebanon)*
Macrophage migration inhibitory factor and innate immunity – *T Calandra (Switzerland)*
Viral immune escape mechanisms – *EJHJ Wiertz (The Netherlands)*

Probiotics

Therapeutic manipulation of the gut flora – *tbc*
Treatment of murine colitis by lactobacillus secreting IL-10 – *L Steidler (Belgium)*
Immunity and probiotics – *tbc*
Helicobacter pylori infections and probiotics – *CE Nord (Sweden)*
Biotherapeutic agents for antibiotic associated diarrhoea – *H Mittermayer (Austria)*

Clinical syndromes I

Antipseudomonas strategies in cystic fibrosis – *N Hoiby (Denmark)*
Prosthesis related infections – can we save the prosthesis? – *W Zimmerli (Switzerland)*
Human ehrlichiosis – *tbc*
Bartonellosis – *D Raoult (France)*
Diffuse panbronchiolitis – *H Kobayashi (Japan)*
Sepsis and septic shock – *N Aikawa (Japan)*

Clinical syndromes II

Group B streptococci: the parasite and the host – *tbc*

Skin and soft tissue infections in compromised hosts – *J Arata (Japan)*
Chlamydial interference with apoptosis – *tbc*
Epidemiology of surgical infections – *tbc*
Prophylaxis of surgical infections – *Y Sumiyama (Japan)*
Infections caused by anaerobes – *tbc*

Development of new antibiotics

The impact of bioinformatics on the discovery of new antibiotics – *tbc*
Enhancing anti-infective drugs discovery – *tbc*
Integration of genomics in antibacterial drug discovery – *H Loferer (Sweden)*
Anti-infective drugs based on the quorum system – *J Stein (Germany)*
Antisense technology for the discovery of anti-infectives – *tbc*
Finding novel classes of antimicrobial compounds – *tbc*

Old drugs, new concepts

The history of antibiotics: the Japanese story – *J Kumazawa (Japan)*
Antifungal drugs – *F Odds (UK)*
Extended spectrum beta lactamases – *M Akova (Turkey)*
Aminoglycosides, any news? – *tbc*
Polymyxins – *tbc*

Problems in antimicrobial resistance

Resistance problems in Europe – *J Verhoef (The Netherlands)*
Surveillance of resistance in Russia – *L Stratchounski (Russia)*
Global surveillance: nationwide molecular based surveillance of resistant bacteria in Japan – *M Inoue (Japan)*
Why is antimicrobial resistance so prevalent in southern Europe? – *tbc*
Why is antimicrobial resistance less prevalent in northern Europe? – *D Monnet (Denmark)*
Problems of antibiotics in the environment – *K Kummerer (Germany)*

Difficult-to-treat meningitis

Pathogenesis and prevention of sequelae of bacterial meningitis – *WM Scheld (USA)*
Meningococcal vaccines – *L Alphen (The Netherlands)*
The impact of antimicrobial resistance on the management of bacterial meningitis – *K Klugmann (USA)*
The pros and cons of dexamethasone therapy in meningitis – *M Täuber (Switzerland)*
Activated protein C in disseminated meningococcal disease – *E Rintala (Finland)*

Clinical trials

The investigation as the weak print – *SR Norrby (Sweden)*
Do we get any help from the regulations? – *tbc*
Drug development guidelines for clinical trials of anti-infective drugs – *K Sunakawa (Japan)*
Guidelines for drug development in the Western world – *J-C Pechère (Switzerland)*
Guidelines for nationwide antibiotic usage – *P Huovinen (Finland)*

Strategies in the hospital to prevent and combat resistance

Strategies to reduce selection and spread of resistance – modelling – *M Bonten (The Netherlands)*
Strategies to reduce selection and spread of resistance – infection control – *tbc*
Strategies to reduce selection and spread of resistance – antibiotic policies – *D Berild (Norway)*
From MRSA to VISA 'molecular insights' – *K Hiramatsu (Japan)*
MRSA, VISA, GISA and VRE epidemiology in a nutshell – *B Murray (USA)*

Tropical disease

Managing resistant malaria – *NJ White (Thailand)*
Managing resistant visceral leishmaniasis – *S Sundar (India)*
Ivermectin for treatment of *Strongyloides stercoralis* – *A Saito (Japan)*
Molecular basis of resistance in malaria – *S Marzuki (Indonesia)*
Pathogenesis of malaria – *W Graninger (Austria)*

AIDS/HIV

Development of an HIV vaccine – *T Hanke (UK)*
Co-receptor usage for HIV therapy – *D Schols (Belgium)*
Cost-effective prevention strategies for vertical transmission – *FA Miiro (Uganda)*
Therapeutic options for developing countries – *JMA Lange (The Netherlands)*
Gene therapy for HIV – *M Wainberg (Canada)*
Antiretroviral therapy: state-of-the-art and future perspectives – *SA Danner (The Netherlands)*
Antiretroviral drug resistance – *CAB Boucher (The Netherlands)*
Metabolic complications in HIV infected patients treated with antiretroviral therapies – *IL Tourraine (France)*
Role of fusion inhibitors – *N Cammack (UK)*
IL-2 as an immunotherapeutic agent – *tbc*
Evolution of HIV – *M Peeters (Belgium)*
The changing epidemic of paediatric HIV infection in Romania – *tbc*
Epidemiology and management of paediatric HIV in the western world – *SPM Geelen (The Netherlands)*
Coinfection of HIV and hepatitis: impact and consequences for management – *V Soriano (Spain)*
Medical assistance for procreation in HIV-infected patients – *D Salmon-Ceru (France)*

Infections in compromised patients

New aspects of infections in neutropenic patients – *K Totsuka (Japan)*
Role of haematopoietic growth factors in the prevention and treatment of infections – *R Feld (Canada)*
Infection prevention in neutropenic cancer patients: do the quinolones and azoles meet our expectations? – *E Bow (Canada)*
Epidemiology and risk factors for fungal infections in neutropenia – *C Viscoli (Italy)*

Clinical impact of new vaccines on clinical practice

Bacterial meningitis – *UB Schaad (Switzerland)*
Otitis media – *R Dagan (Israel)*
Community acquired pneumonia – *K Klugmann (USA)*
Urinary tract infections – *L Langermann (USA)*
Lyme borreliosis – *tbc*

New technologies in microbiology

Microbial genomics; from sequence to function – *tbc*
Fish in microbiology – *VAJ Kempf (Germany)*
Raman resonance spectroscopy of microbes – *GJ Puppels (The Netherlands)*
Detecting unculturable bacterial populations – *AD Akkermans (The Netherlands)*
Clinical impact of novel, rapid PCR diagnostic tests – *M Bergeron (Canada)*

Travel medicine

New zoonotic paramyxoviruses: the Nipah experience in Malaysia – *JM Yong (UK)*
STDs in the traveller – *tbc*
Dengue vaccines: promises + challenges – *MJ Cardosa (Malaysia)*
New tools for diagnostic work-up of travel; associated parasitosis – *T Gool (The Netherlands)*
Managing resistant typhoid fever – *TT Hien (Vietnam)*

Food and waterborne diseases

Legionellosis in tropical countries – *I Gerstenblut (The Netherlands)*
Epidemiology of *L. pneumophila* – *tbc*
BSE and variant CJD in Europe – *RG Will (UK)*
Strategies for the reduction or elimination of *Campylobacter* from the food chain – *D Newell (UK)*
Water safety initiatives of the WHO – where does it stand? – *tbc*

Tuberculosis, the agent and the disease

Virulence, transmission and pathogenesis – *PD Helden (South Africa)*
Why is TB out of control? – *tbc*
Importance of drug resistant organisms – *tbc*
Progress in global tuberculosis control: from DOTS implementation to epidemiological impact – *C Dye (Switzerland)*
Tuberculosis the agent, the host response and the disease – *SHE Kaufmann (Germany)*

Micro-organisms and chronic diseases

Is atherosclerosis an infectious disease? – *PJ Cook (UK)*
Micro-organisms and sarcoidosis – *tbc*
Guillain–Barré syndrome and *Campylobacter* – *HP Endtz (The Netherlands)*
Multiple sclerosis and viruses – *tbc*
Trophyrema whippelii: any news? – *tbc*

Life-threatening CAP in symposia on pneumonia during the last decade

CAP: aetiology and microbial investigations – *T File (USA)*
CAP: risk stratification and site of care – *tbc*
Community acquired pneumonia: the role of macrolides – *H Kobayashi (Japan)*
Japanese guidelines for community-acquired pneumonia – *T Matsushima (Japan)*
Diagnosis and treatment of ventilator-associated pneumonia – *JY Fagon (France)*
European view on pneumonia – *IM Hoepelman (The Netherlands)*

Emerging infections and problems

Bioterrorism – *tbc*
Non-human usage of antibiotics – *tbc*
New rickettsial diseases – *D Raoult (France)*
West Nile fever – virus – *E Rubinstein (Israel)*
Hantavirus infections – *A Papa (Greece)*

ISC commission for UTI in collaboration with FESCI

Pathogenicity islands of uropathogenic *E. coli* and evolution of virulence – *J Hacker (Germany)*
Host responses in the urinary tract – *CM Svanborg-Eden (Sweden)*
Pathogenesis of bacteriuria in women with diabetes mellitus – *IM Hoepelman (The Netherlands)*
Does PK/PD apply to UTI? – *N Frimodt-Moller (Denmark)*
Significance of bacterial resistance for outcome of UTI – *WE Stamm (USA)*

Recent progress in aspergillosis and antifungal therapy: joint symposium of the ISC and the International Immunocompromised Host Society (ICHS)

New diagnostic tools – *PE Verweij (The Netherlands)*
Epidemiology and control of aspergillosis – *E Anaissie (USA)*
Antifungal therapy – *T Walsh (USA)*
Adjunct therapy for fungal infections – *BJ Kullberg (The Netherlands)*
New antifungal drugs in development: lipopeptides – *S Kohno (Japan)*

LIBRA* ~ a new initiative for promoting the appropriate use of antibiotics

Despite all the publicity about antibiotic resistance, a recent study showed that a significant proportion of primary care physicians prescribe antibiotics without an approach that maximizes the effectiveness, and minimizes treatment failure due to resistance. Many community doctors do not consider that antibiotic resistance is a concern for them. Primary care physicians are aware of educational initiatives, but the implementation of appropriate antibiotics is not yet fully developed. Bayer AG supports the establishment of a new international appropriate-use initiative called LIBRA that will address these problems.

Aims of LIBRA

The main aims of the LIBRA initiative are to:

- Reduce inappropriate prescribing of antibiotics;
- Encourage antibiotic use that:
  - Maximizes therapeutic outcome;
  - Minimizes resistance development;
  - Reduces the health economic burden that is associated with infectious disease.

The LIBRA initiative:

- Developing education programmes targeted separately at the general public and doctors;
- Working with key individuals in political, medical and public spheres to promote changes in antibiotic usage;
- Supporting evidence-based guidance on the appropriate selection and use of antibiotics.

Study of doctors' prescribing practices

The need for the LIBRA initiative was highlighted by a study commissioned by Bayer AG and conducted in France, Germany and the USA. The study was undertaken to get a better understanding of doctors' prescribing practices, in relation to antibiotic resistance, treatment failure and their views on the appropriate use of antibiotics.

The study was conducted in the latter half of 2000. The primary care physicians interviewed (over the telephone) all had direct experience of prescribing antibiotics on a regular basis. One hundred interviews were conducted in France, 100 in Germany and 250 in the USA.

Key findings of survey

- Many doctors are taking a trial and error approach to antibiotic prescribing and do not see resistance as a cause of treatment failure;
- Doctors have varied views on what is inappropriate use of antibiotics. Over-prescription was cited by 31%, failure to select correct antibiotics for the infection by 28%, and not matching the choice of antibiotics to the severity of infection by 24%. Ignoring resistance was mentioned by only 2% of respondents.

The study showed that in the main, primary care physicians have experience of antibiotic resistance, but do not perceive it as a problem for their own individual practice.

Inappropriate antibiotic use was regarded as being due to extraneous factors over which the doctors had little control, such as poor patient understanding and compliance, and the pressure to initiate treatment with incomplete clinical information being available. The main themes to emerge from the research were that:

- Doctors do experience cases of antibiotic resistance, which can be as high as one in five among patients receiving first-line therapy, but perceive it not to be a problem for their individual practice;
- Education guidance and programmes flexible to local needs were very welcomed, for both themselves and the community.

Antibiotic prescribing and resistance

Nineteen per cent of patients had organisms showing antibiotic resistance during first-line therapy (range 9% in USA to 19% in Germany), which fell to 14% in second-line therapy. Eighteen per cent of respondents in France diagnosed resistance through culture and sensitivity testing, while the figure in Germany was 73% (Figure 1).

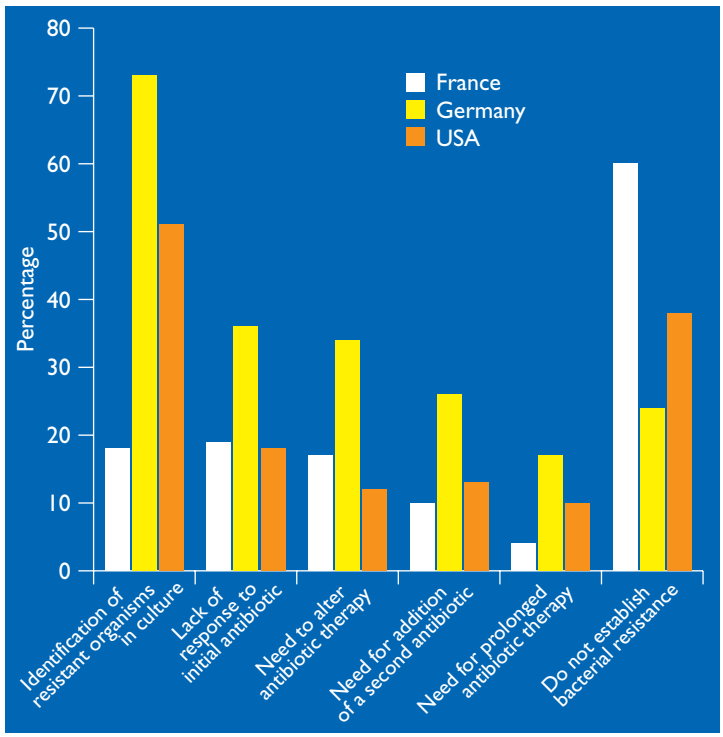

Figure 1: Approaches by primary care physicians (%) in establishing bacterial resistance.

The primary care physicians surveyed failed to differentiate between true resistance and non-response as the cause of treatment failure; 22% chose to confirm the presence of resistant organisms by requesting bacterial cultures and/or making further diagnoses. When there was treatment failure 71% switched patients onto another antibiotic.

The need for better education

One-third of doctors were aware of efforts to promote the appropriate use of antibiotics (USA 39%, Germany 18% and France 30%). Of these responders only about one-half used such resources.

Medical organizations were seen as the main source of such programmes by 50% of primary care physicians in France and 17% in Germany (where 44% tended to look more to pharmaceutical companies for information).

When the physicians were asked 'who needs more education?', 23% said the public, 8% said doctors themselves and 51% did not comment.

Conclusions

There is great variation in the understanding by primary care physicians of the correct use of antibiotics, and its association to resistance. Variation was also seen between countries. A programme such as LIBRA may be able to help in enhancing a more coherent concept of appropriate prescribing of antibiotics.

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*More information about LIBRA is available on its website: www.librainitiative.com

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Opinion ~ the trouble with breakpoints

Breakpoints are increasingly taken as definitive boundaries. There is much to commend in this: arbitrary definitions of resistance are dismissed, inappropriate therapies discouraged, and data from remote sites can be pooled for surveillance. However, rules carry risks – many individuals use them as alternatives to thought and a few exploit their anomalies.

Microbiological, pharmacological or clinical criteria?

Before supporting these assertions, it should be understood that breakpoints can be set from microbiological, pharmacological or clinical criteria – sometimes giving different values.

A microbiological breakpoint distinguishes organisms with and without acquired resistance, irrespective of drug levels in the patient. Pharmacological breakpoints aim to ensure a sufficient excess of serum drug over minimal inhibitory concentration (MIC). Beta-lactams require a concentration above MIC for around 40% of the dosage interval; quinolones an area under the curve (AUC):MIC ratio of >125 for Gram-negative or >30 for Gram-positive infections; and aminoglycosides a high C_{max}:MIC ratio.[1]

Clinical breakpoints relate MICs to response – they are ideal but difficult to establish, since it is unethical to use a drug when microbiological or pharmacological criteria predict failure.

The level at which a breakpoint is set varies on the weight placed on these different criteria and on time, the agency, and the ascendancy of proponents.

Pharmacological criteria and false susceptibility

The best-known category of problem arises when isolates with defined mechanisms of resistance appear 'susceptible' at breakpoints set on pharmacological criteria. Breakpoints of 8–16 mg/l for cephalosporins notoriously allow extended-spectrum beta-lactamase (ESBL) producers to appear susceptible.[2] Breakpoints of 64 mg/l for ureidopenicillins are dubious when MICs for 'wild-type' enterobacteria and pseudomonads are 1–4 mg/l, and when MICs of 16–64 mg/l predict the presence of acquired beta-lactamases[2] and clinical failure.[3] Then there are carbapenem breakpoints of 4–8 mg/l for enterobacteria, when MICs for metallo-beta-lactamase producers may only be 1–4 mg/l.[4,5]

Mixed criteria

Another problem arises when breakpoints chosen on different criteria are mixed. Take penicillin and pneumococci, where:

- MICs ≤0.06 mg/l indicate susceptibility;
- MICs 0.12–1 mg/l indicate intermediate resistance;
- MICs ≥2 mg/l indicate full resistance.

The 0.12 mg/l breakpoint is microbiological, but predictive for meningitis. The 2 mg/l breakpoint was thought predictive in respiratory infections and bacteraemia, but high-dose penicillin often remains effective in these settings versus pneumococci with MICs of 2 mg/l.[6] Co-amoxiclav and some cephalosporins have similar antipneumococcal activity (±1 dilution) to penicillin and are affected by the same resistance mechanism, but are not graded against a biological breakpoint. Rather, their 'low' breakpoints are 0.5–1 mg/l.

Hence, a recent question I was asked from the audience in Thailand: 'Company X, say only 20% of pneumococci are resistant to their beta-lactam, but 60% are resistant to penicillin. How about that?' I desperately wondered if beta-lactamases had reached Thai pneumococci, but responded: 'Which breakpoints?' The reply was: '0.12 mg/l for penicillin, 1 mg/l for their compound'.

Whether their compound would be any better than high-dose penicillin in respiratory infection is doubtful, but it would cost more.

One answer is to abandon the low breakpoint; the US Centers for Disease Control and Prevention (CDC) proposes penicillin breakpoints of 1 mg/l and 4 mg/l for pneumococci.[7] Switching to the higher breakpoint will, however, cause a precipitate fall in the apparent prevalence of resistance. Will someone claim credit? Even if they do not, imagine when journalists ask: 'last year, 10% of *pneumonia superbug* isolates were resistant, and now it's only 1%, why?' I'll say: 'because we changed the rules.'

Table 1: Quinolone 'susceptibility' and 'resistance' in some borderline *E. coli*

		MICs (mg/l) and susceptibility categorization			
Compound	Breakpoints, (NCCLS)[a]	*E. coli* ATCC 25922 (control)	Isolate 1	Isolate 2	Isolate 3
Ciprofloxacin	1/4	0.004–0.016	2 (I)	4 (R)	2 (I)
Ofloxacin	2/8	0.016–0.12	2 (S)	4 (I)	8 (R)
Levofloxacin	2/8	0.016–0.12	1 (S)	2 (S)	4 (I)
Norfloxacin	4/16	0.03–0.12	4 (S)	16 (R)	4 (S)

[a]MICs ≤low value, susceptible (S); MICs ≥high value, resistant (R); MICs between values, intermediate (I).

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Moreover, the change will hide isolates – with raised MICs – perhaps *en route* to resistance; and which, if in the meninges, should not be treated with penicillin G.

Borderline MICs

A third problem arises when the MICs of related drugs cluster around their breakpoints. Table 1 shows MICs of fluoroquinolones for recent *Escherichia coli* isolates. To a biologist, the isolates are resistant compared with the control; nevertheless, they are variously susceptible, intermediate and resistant at breakpoint. Is this right:

- When MICs are subject to ±1 dilution experimental variation;
- When the AUC:MIC ratios needed with fluoroquinolones remain under debate;
- When, for typhoid, ciprofloxacin MICs of 0.25 mg/l predict failure or delayed cure?[8]

Surely, it would be better to say that the isolates (Table 1) are intermediate to all quinolones and to identify the least-bad analogue? This might also mitigate the desires of manufacturers to 'get' breakpoints a little higher than their competitors.

The example of linezolid

Misplaced faith in MIC precision can lead to bad breakpoints in the first place, too. Linezolid presents an

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example. Those who have studied linezolid find its MICs unimodal and tightly packed, but some mostly find MICs of 1 mg/l[9] for most staphylococci and enterococci, whereas others mostly find 4 mg/l.[10] Pharmacodynamics suggest a breakpoint of 4 mg/l or 8 mg/l. For one indication, however, Phase III data showed an insignificantly poorer response against staphylococci with MICs of 4 mg/l. Elsewhere, linezolid was equally efficacious against staphylococci with MICs of 2 mg/l and 4 mg/l. The UK Medicines Control Agency identified a 'general breakpoint' of 2 mg/l, while noting: 'limited evidence that staphylococci and enterococci with MICs of 4 mg/l will respond.' Others* have favoured a breakpoint of 4 mg/l. However, suppose 2 mg/l sticks? Are workers who generally find MICs of 4 mg/l going to say that linezolid is inactive against most staphylococci and enterococci, whereas others will find it universally active against identical bacteria?

Standardization is not the solution

Some will say that the answer lies in more standardization, and in perfection of breakpoints. Complete standardization is, however, impossible so long as there is more than one supplier of media and so long as media are natural products. Even in highly standardized tests, MICs vary ±1 dilution. Thus, problems will persist whenever a breakpoint cuts the upper end of a normal susceptibility distribution. Moreover, standardization cannot overcome the problems outlined for beta-lactams against pneumococci, which arise from philosophical differences in how breakpoints are set. Worse, *standardization encourages conviction without guaranteeing validity.*

Thought and interpretation

What are needed are *thought* and *interpretation*, not slavish belief. This is heresy, but there are hopeful signs. Expert rules and interpretive reading systems are incorporated in many of the automated susceptibility-testing systems and zone readers. These interpret the susceptibilities and resistance to batteries of related antibiotics, infer the resistance mechanisms, and then edit the remaining susceptibilities based on these inferences. Thus, an isolate inferred to have an ESBL but found to be 'susceptible' (cf. breakpoint) to cefotaxime would have this result edited to 'resistant'. Such systems must, perforce, recognize the perverse effects of dubious breakpoints. It would be ironic if they led to better interpretation in routine laboratories than in resistance surveys, performed with high quality MIC tests but with unthinking application of mandated breakpoints.

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*European Committee on Antimicrobial Susceptibility Testing (EUCAST), British Society for Antimicrobial Chemotherapy (BSAC) and, for staphylococci, the US National Committee for Clinical Laboratory Standards (NCCLS).

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journal, but which sensibly limit how they can be applied. It is clearly inappropriate to use them to rank all types of journals in all subject areas, and even comparing the same type of journal in the same subject category. The use of journal impact factors for evaluating individual scientists is even more dubious, given the statistical and sociological variability in journal impact factors.

The numerator/denominator problem

What exactly counts as a paper? Do letters to the editor count? Only those classified as 'articles' or 'reviews' are counted in the denominator, whereas citations to all papers are counted for the numerator. This can lead to an exaggerated impact factor. This is yet another example of why considerable care needs to be taken when using impact factors.

Conclusions

Impact factors are only one of a number of measures for describing the 'impact' that particular journals can have. The value is affected by the subject area, type and size of a journal, and the 'window of measurement' used. Use of the absolute values of impact factors, outside of the context of other journals within the same subject area, is quite meaningless. Extending the use of the journal impact factor from the journal to the authors of papers in the journal is highly suspect; the error margins can become so high as to make any value meaningless. Impact factors are useful in establishing the influence journals have within the literature of a discipline. They are not, however, a direct measure of quality and must be used with considerable care.

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